REMARKS

Entry of the foregoing and reconsideration of the above-identified application, in light of the remarks which follow, are respectfully requested.

Claims 6 and 21 have been amended to recite that the substance recited in the claims is "continuously" administered in an amount "effective for reducing heart weight and not effective for said diuretic and hypotensive effects." Claim 21 has also been amended, similar to claim 6, to recite that the substance is "continuously" administered and that chronic heart failure is treated "by reducing heart weight not based on diuretic and hypotensive effects." Support for the amendments may be found at the very least at page 13, lns. 2-4 and 9-10; page 14, line 34 - page 15, line 5; page 16, lns. 1-3 and 8-12. page 19, line 35 - page 20, line 11; page 21, line 25- page 22, line 2. No new matter has thus been added. No new issues have been raised by these amendments and entry thereof is consistent with §1.116.

Claims 1-5 and 15-20 have been deleted and new claims 22-27 have been added. The deleted claims had been withdrawn from consideration by the Examiner. Applicants reserve the right to file a divisional application directed to these claims. The newly added claims specify that the effective amount is "an amount sufficient to achieve a plasma level of about 0.5 ng/mL." Support for this recitation may be found at the very least at page 14, lns. 16-18. Claims 24 and 25 further specify that the active ingredient is continuously administered for at least one week. Support for this amendment may be found at the very least at page 13, lns. 2-4 and 9-10, and page 16, lns. 1-3 and 8-12. New claims 26 and 27 recite that "the effective amount is 0.025 μg/kg/min in a human." Support for these claims

may be found at the very least at page 13, lns. 2-4 and 9-10, and page 16, lns. 1-3 and 8-12. One skilled in the art wold recognize, as explained in more detail *infra*, that a plasma level of about 0.5 ng/mL is achieved in a human by administration of 0.025 μg/kg/min of the active substance. No new matter has thus been added. No new issues have been raised by these amendments and entry thereof is consistent with §1.116.

Prior to addressing the rejections of record, applicants' invention will first be discussed. As recited in the claims, Applicants' invention is directed to a method for treatment of cardiac hypertrophy and chronic heart failure. Administration of a substance which acts on guanylyl cyclase A, a receptor for natriuretic peptide, and accelerates the production of cGMP, was found to produce a decrease in cardiac weight and thus treat cardiac hypertrophy. As now recited in the claims, the amount administered for these effects are *not* effective amounts for diuretic and hypotensive effects.

Applicants experimentally proved that the active component of the present invention, such as ANP, not only inhibits cardiac hypertrophy, but also decreases the cardiac weight even after the establishment of the cardiac hypertrophy. In addition, this medical effect is exhibited at a dose level which does not produce a change in blood pressure or urine volume, i.e., does not produce a diuretic or hypotensive effect. *See, e.g.,* Example 1, paragraph bridging pages 14-15 and Figure 1. This shows that the present invention directly acts on the heart to prevent or inhibit cardiac hypertrophy, and does not act through natriuretic action or hypotensive action provided by the active component, such as ANP.

In their experiments, Applicants used high blood pressure model animals and volume load model animals. These experiments also confirmed that even after cardiac hypertrophy was established, administering the active components of the invention decreased the hypertrophy. *See, e.g.,* Example 2, pages 15-18.

Claims 6, 8-10, 21 have been rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Blaine et al (US Patent No. 4,652,549), as evidenced by Espiner (which is admittedly not prior art). According to the Examiner, Blaine teaches treatment of cardiac hypertrophy using atrial natriuretic peptide (ANF) and fragments thereof. Based upon Espiner, it is allegedly well known that ANF and analogs thereof stimulate guanylate cyclase A and production of cGMP. The effects of ANF as instantly claimed are thus allegedly inherently present. This rejection is respectfully traversed.

Claims 6, 8-10 and 21 have been rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Neustadt et al (US Patent No. 5,356,925). According to the Examiner, Neustadt et al teaches treatment of cardiovascular disorders (e.g., hypertension, congestive heart failure, renal insufficiency) using a combination of natriuretic peptide(s) and ACE inhibition. The Examiner asserts that it was well known that ANF and analogs thereof stimulate guanylate cyclase A and production of cGMP. The treatment of cardiac hypertrophy using atrial natriuretic peptide (ANF) analogues which bind to natriuretic receptor is thus asserted to be inherently present. This rejection is also respectfully traversed.

Claims 6, 8, 9 and 21 have been rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Berman et al (JP 63303998) as evidenced by Espiner. The Examiner asserts that Berman et al teaches treatment of cardiac hypertrophy using atrial natriuretic peptide

(ANF) analogues which bind to natriuretic receptor. According to the Examiner, it is "well known that ANF, as well as its analogs stimulate guanylate cyclase A and production of cGMP." The effects of ANF analogues as claimed are thus concluded to be inherently present. This rejection is also respectfully traversed.

Claims 6 and 11-14 have been rejected under 35 U.S.C. §103(a) as allegedly being obvious over Blaine or Berman or Neustadt. The Examiner alleges that it would have been obvious to one skilled in the art to modify the cited art to arrive at Applicant's claimed invention. This rejection is also respectfully traversed.

Claims 6, 8-14 and 21 have been rejected under 35 U.S.C. §103(a) as allegedly being obvious over Blaine or Berman or Neustadt in view of Cao (Hypertension 25:227-34 (1995)). The primary references are cited as teaching treatment of cardiac hypertrophy by natriuretic peptides, but are acknowledged to "not specifically teach that the effect achieved as a result of the treatment include reduction of heart weight by a mechanism not based on diuretic or hypotensive effect." (Page 7). Cao is cited as teaching that (1) cardiac hypertrophy include stimulation of gene cascade; (2) natriuretic peptides reduce stimulation of this cascade, as evidenced by a decrease in thymidine incorporation; and (3) demonstrates that the hypertrophy-reducing effect of the natriuretic peptides is due to their interaction with guanylyl cyclase A natriuretic peptide receptor and is further mediated by formation of cGMP. The Examiner alleges that it would have been obvious to one skilled in the art that cardiac hypertrophy can be reduced by natriuretic peptides by interference with gene activation and that the effect of treating cardiac hypertrophy described in the methods might

have included the mechanism of the claimed invention. This rejection is also respectfully traversed.

Each of the above-identified rejections made in the Official Action is respectfully traversed. None of the cited references disclose or even suggest the instantly claimed methods. None of the cited references disclose or even suggest that heart failure can be treated by reduction of the heart weight, using a substance that acts on guanylyl cyclase A natriuretic peptide receptor, as recited in the claims. Nor do the references disclose or even suggest that an amount could be used for treatment, which amount is effective for reducing heart weight but is not effective for diuretic and hypotensive effects. The effective amount for the instantly claimed method is much lower than what is needed to produce diuretic and hypotensive effects. *See,* Example 1.

Since the amount used in the claimed method is much lower than what is has previously been used in the art, none of the cited references inherently produce the claimed method, as alleged in the Official Action. For example, in Examples 1 and 2 of the application, an effective amount is 0.1 μg/kg/min was used for administration to a rat. This dosage resulted in a plasma level of about 0.5 ng/mL (= 507 pg/mL, *see,* p.14, l.17). This plasma level is confirmed in Hayashi et al, *Applied Pharmacology*, 49(3): 287-311 (1995) (copy enclosed). Table 4 (p.295) of Hayashi et al shows that the dose of 0.1 μg/kg/min provides a plasma level of 0.60 ± 0.09 ng/mL, which is approximately the same as "about 0.5 ng/mL," as disclosed in the instant application.

Obata et al, *Jpn. Pharmacol. Ther.*, 21(3): 129 (1103) - 140 (1114) (copy enclosed), shows in Fig. 6 and Table 2 (p.137 (1111)) that a dose of Carperititde of 0.1

μg/kg/min in humans provided a plasma level of 2120 $\pm$ 440 pg/mL. This plasma level is converted to about 2.1 ng/mL.

Maeda et al, *Japanese Circulation Journal*, 63: 816018 (1999), discloses that a plasma level of about 0.5 ng/mL (= 560 pg/mL) was provided by administration of ANP at a rate of 0.025 μg/kg/min. *See,* p. 817, 1st column. Moreover, Maeda et al confirms that administration of such an effective amount of the active ingredient did not significanly change blood pressure, heart rate or urinary volume. *See,* p. 817, 1st column and Fig. 1.

Thus, a dose of about 0.1 μg/kg/mL provides a plasma level of about 0.5 ng/mL in a rat and about 2.1 ng/mL in a human. That is, the same dose provides a 4-times higher plasma level in a human in comparison with a rat.[1] Therefore, one skilled in the art would recognize that the "effective amount" of 0.1 μg/kg/min used in Examples 1 and 2 for a rat corresponds to an "effective amount" of 0.025 μg/kg/min in human.

The cited references fail to disclose such an "effective amount," as recited in the instant claims. For example, Blaine teaches a dosage of 10 - 2000 p moles/kg/min, which corresponds to 0.03 - 6 μg/kg/min" since the molecular weight of hHANP is 3080. Blaine et al thus fails to teach an "effective amount" as required by applicants' claims.

In addition, none of the cited references teach "continuously" administering the active ingredient as now recited in the claims. None of Blaine, Neustadt or Berman teaches continuous administration of the active ingredient as instantly claimed.

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[1]Hayashi et al also shows in Table 4 (p.295) that a dose of 0.4 μg/kg/min in a rat provides a plasma level of about 2.95 ng/mL. This plasma level corresponds to "about 2.1 ng/mL," that is provided by the dose of 0.1 μg/kg/min in a human. Again, the "effective amount" in a human is one-fourth that required for a rat to obtain the same plasma level.

Nor do any of the references disclose or suggest that chronic heart failure could be treated in addition to treatment of cardiac hypertrophy, as instantly claimed. To be able to treat heart failure by reduction of heart weight in addition to treating cardiac hypertrophy is very advantageous. The instantly claimed method recited in claim 21 is particularly advantageous in view of the fact that the active ingredient of applicants' invention exhibit inhibitory effects on hypertrophy and pulmonary congestion at dose levels at which it does not affect blood pressure, heart rate or urine volume:

> In addition, since ANP exhibited inhibitory effects on cardiac hypertrophy as well as pulmonary congestion ameliorating effects in a volume-loaded hypertrophy model, it was suggested that ANP is also effective in the case of using in patients with pulmonary congestion, a major symptom of chronic heart failure and a cause of dyspnea. Moreover, since ANP exhibits inhibitory effects on hypertrophy and pulmonary congestion at dose levels at which it does not affect blood pressure, heart rate or urine volume, it has few adverse side effects in terms of hemodynamics and is considered to be able to be used safely.

See, page 21, lines 13-24.

In addition, there is a strong need in the art for such a method for treating heart failure. As described in the specification:

> Based on these results, ANP was strongly suggested to be able to improve cardiac hypertrophy based on high blood pressure, valvopathy or myocardial infarction, as well as pulmonary congestion that occurs as a result of cardiac dysfunction. Cardiac hypertrophy is itself an independent risk factor for ischemic heart disease, arrhythmia and chronic heart failure, while chronic heart failure in particular is a disease having a high mortality rate and poor prognosis. Accordingly, under the present circumstances in which there is an extremely dire need for a new drug that is effective in improving cardiac hypertrophy and ameliorating the load on the heart, the pharmaceutical composition for treatment of heart disease based on cardiac hypertrophy as claimed in the present invention is extremely useful.

See, page 21, line 25 - page 22, line 2.

It should be noted that, except for patients suffering hypertension, in many cases patients with heart failure have a blood pressure lower than normal. Therefore, the instantly claimed method can be used and the active ingredient administered as claimed at a level that does not affect the blood pressure, but causes involution of cardiac hypertrophy that can be universally used in clinical trails.

One skilled in the art would not have predicted from any of the cited references that the instantly claimed active ingredient could be used at such low levels that no diuretic or hypotensive effects are produced, but that the active ingredient would still antagonize angiotensin and affect other factors involved in cardiac hypertrophy and thus reduce heart weight. For example, in the Cao et al reference cited in the Official Action, ANP at a concentration of 10^{-6} M was found to inhibit the growth of cardiac fibroblast cells only by about 30%. This concentration is about 1,000 times higher than the blood levels of ANP contemplated in applicants' invention. Such high ANP concentrations would fall *outside* the instantly claimed methods since the much higher ANP concentrations would produce diuretic and hypotensive effects. Moreover, for the reasons discussed *supra*, such higher concentrations would not be as useful for treating cardiomyopathy or heart failure as claimed by applicants.

Additional art, copies of which are enclosed herewith, confirm that the effective amounts of applicants invention do not produce diuretic and hypotensive effects. For example, Saito et al, *Circulation* 76(1): 115-124 (1987), discloses that ANP infusion at a rate of 0.1 μg/kg/min has both vasorelactant and diuretic actions. *See,* p. 121, left column, lns. 9-11 from the bottom.

Hayashi et al, *Journal of the American College of Cardiology*, 37(7): 1820-1826 (2001) further shows that an ANP starting dose of 0.025 μg/kg/min has only a mild effect on the reduction of the preload and blood pressure (*see,* p. 1823, right column, lns. 17-20). Table 2 shows that a reduction of blood pressure was as small as only 5 mm Hg, and reduction of PCWP was as small as about 2.5 mm Hg.

As described above, none of the references disclose Applicants' claimed method of treatment. Nor would such a method as claimed be obvious based upon the cited art. There is no reason for one skilled in the art to expect, based upon Blaine, Berman or Neustadt, that a substance that acts on guanylyl cyclase A natriuretic peptide receptor and accelerates production of cyclic guanosine monophosphate can be administered in an amount that is not effective for diuretic and hypotensive effects on reducing heart weight and is able to treat cardiac hypertrophy which is not based on diuretic and hypotensive effects.

New claims 22-25 further distinguish over the cited art. As described *supra*, none of the cited references disclose continuous administration of the active ingredient for any time period, much less for at least one week. Nor do the references disclose that an effective amount should achieve a plasma level of about 0.5 ng/mL.

In view of the above, withdrawal of the rejection is respectfully requested and believed to be in order.

In the event that there are any questions relating to this amendment, it would be appreciated if the Examiner would contact the undersigned attorney at 508-339-3684.

Further and favorable action in the form of a Notice of Allowance is respectfully requested and believed to be in order.

Respectfully submitted,

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Marked-up Claims 6 and 21

6. (Twice Amended) A method for treatment of cardiac hypertrophy by reducing heart weight not based on diuretic and hypotensive effects comprising continuously administering a substance that acts on guanylyl cyclase A natriuretic peptide receptor and is able to accelerate production of cyclic guanosine monophosphate, to a subject in need of such treatment in an amount effective for reducing heart weight and not effective for said diuretic and hypotensive effects [treating said cardiac hypertrophy].

21. (Amended) A method for treatment of chronic heart failure by reducing heart weight not based on diuretic and hypotensive effects comprising continuously administering a substance that acts on guanylyl cyclase A natriuretic peptide receptor and is able to accelerate production of cyclic guanosine monophosphate to a subject in need of such treatment in an amount effective for [treating said chronic heart failure] reducing heart weight and not effective for said diuretic and hypotensive effects.